IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS L.L.C., ONO PHARMACEUTICAL CO., LTD., and TASUKU HONJO,	)	
Plaintiffs,	)	
v.	)	C.A. No. 17-1027 (GMS)
GENENTECH, INC.,	)	**JURY TRIAL DEMANDED**
Defendant.	)	

ANSWER AND COUNTERCLAIMS OF DEFENDANT GENENTECH, INC.

Defendant Genentech, Inc. ("Genentech") answers the Complaint of Plaintiffs Bristol-Myers Squibb Co., E. R. Squibb & Sons, LLC, Ono Pharmaceutical Co., Ltd., and Tasuku Honjo (collectively, "Plaintiffs") as set forth below. Numbered paragraphs below correspond to the numbered paragraphs in Plaintiffs' Complaint. Genentech denies all allegations contained in the Complaint that are not specifically admitted below.

INTRODUCTION[1]

1. Genentech admits that more than one million people in the United States are diagnosed with cancer each year according to the American Cancer Society. Genentech denies however, that cancer is a single disease that proceeds in a single fashion, as Plaintiffs' Paragraph 1 suggests. Plaintiffs' description of the role of the immune system in fighting cancer, and of cancer cells' alleged "ability to 'turn off' or evade the immune system" is not wrong, but it is incomplete and too brief to be entirely accurate, and Genentech reserves its right to disagree with details of this paragraph through experts and fact discovery. Likewise, the allegation that

[1] Genentech generally repeats the headings of the Complaint for the Court's convenience, without adopting them for their substance.

"[c]ancer treatments are therefore developed to decrease tumor growth and metastasis" vastly oversimplifies the process of cancer-therapy development. On that basis, Genentech denies the remaining allegations of Paragraph 1.

2. Genentech admits that this case relates to Genentech's Tecentriq®, a groundbreaking treatment for cancer that falls within the field of immunotherapy. Genentech admits that the treatment of cancer using immunotherapy agents was a scientific breakthrough, but denies any implication that Plaintiffs are responsible for that breakthrough. Genentech admits that some immunotherapy agents work in part by permitting "a patient's immune system to eliminate cancer cells," but denies that this brief statement accurately captures the complex way in which Tecentriq® or any other immunotherapy works in those patients for whom treatment is effective.

3. Paragraph 3 provides a generally accurate overview of certain functions of certain T cells in the human immune system. Reserving its right to disagree with details of this paragraph through experts and fact discovery, Genentech in substance admits the general allegations of Paragraph 3.

4. Paragraph 4 provides a generally accurate, although incomplete, overview of certain PD-1/PD-L1 interactions. Reserving its right to disagree with details of this paragraph through experts and fact discovery, Genentech in substance admits the general allegations of Paragraph 4.

5. Genentech admits that the asserted U.S. Patent No. 9,402,899 (the '899 patent) purports to claim methods of treating tumors by administering anti-PD-L1 antibodies as set forth more fully in the claims of that patent, but denies that the '899 is valid, denies that the named inventors of the '899 patent were the first to teach treatments for cancer and enhancing immune

responses by administering anti-PD-L1 antibodies, denies that the '899 patent shows that "types of anti-PD-L1 antibodies . . . inhibit the interaction between PD-1 and PD-L1," and otherwise denies all other allegations of Paragraph 5.

6. Genentech admits that it is aware of the '899 patent. Genentech further admits that U.S. Patent Application No. 14/726,329 references anti-PD-L1 antibody MDX-1105 and anti-PD-1 antibody nivolumab. Genentech denies that nivolumab—an anti-PD-1 antibody—is an "invention" claimed by the '899 patent. Genentech lacks knowledge or information sufficient to form a belief as to whether either nivolumab or MDX-1105 is the result of the work of all of the named Plaintiffs here and, on that basis, denies the allegation that nivolumab is "Plaintiffs' anti-PD-1 antibody" and that MDX-1105 is "Plaintiffs' . . . anti-PD-L1 antibody." Genentech denies any remaining allegations of Paragraph 6.

7. Genentech admits that Tecentriq®, an anti-PD-L1 antibody, is used in methods of treating certain cancers and that Tecentriq® can enhance a patient's immune response to those cancers as set forth in the full prescribing information for Tecentriq®, and otherwise denies the allegations of Paragraph 7.

8. Genentech admits that both Tecentriq® and Opdivo® (nivolumab) currently have at least some overlap in approved indications for use in the United States, but denies that Genentech and "Plaintiffs" are competitors in the field of immunotherapy, and otherwise denies the allegations of Paragraph 8.

9. On information and belief, Genentech denies that Plaintiffs "invented" "anti-PD-1 antibodies" generally. On information and belief, Genentech admits that Opdivo® was the first anti-PD-1 antibody approved for use anywhere in the world for cancer treatment, and was the first anti-PD-1 antibody approved in the United States for the treatment of a lung cancer.

Genentech lacks knowledge or information sufficient to form a belief as to whether all of the "Plaintiffs" are responsible for the development of Opdivo® and, on that basis, denies the allegation. Genentech otherwise denies the allegations of Paragraph 9.

10. On information and belief, Genentech admits that nivolumab is a monoclonal antibody that binds to PD-1. On information and belief, Genentech notes that according to the Opdivo® (nivolumab) label, "Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth." To the extent that Plaintiffs' paragraph 10 is inconsistent with the label for Opdivo®, Genentech lacks knowledge or information sufficient to form a belief as to the truth of the allegations, and on that basis denies them.

11. Genentech denies that it was clinical testing of nivolumab that "confirmed the remarkable promise of checkpoint inhibitors as targets of immunotherapy," and lacks knowledge or information sufficient to form a belief regarding how "rigorous" the testing of nivolumab was. Genentech admits that on July 4, 2014, Japanese regulatory authorities approved nivolumab for the treatment of melanoma, and on December 22, 2014, the FDA approved nivolumab for the treatment of advanced melanoma in the United States. Genentech otherwise denies the allegations of Paragraph 11.

12. Genentech lacks knowledge or information sufficient to form a belief as to whether any or all of "Plaintiffs" have continued the worldwide development of nivolumab, but admits, on information and belief, that nivolumab is being studied for the treatment of cancers, including the cancers listed in Paragraph 12. With respect to those allegations relating to Phase

III clinical data for nivolumab, the results of those trials speak for themselves and Genentech denies any allegations inconsistent with those results. Regarding FDA approval, Genentech, on information and belief, denies that the BLA for Opdivo® is "Plaintiffs'" BLA. Genentech further lacks knowledge or information sufficient to form a belief regarding FDA's reasons for accepting the BLA for nivolumab other than what has been stated by FDA, and therefore denies any allegations inconsistent with FDA's statements. Genentech admits that nivolumab is now approved for use in "patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy" as set forth in the label for Opdivo®. Genentech denies any allegation that it was nivolumab that demonstrated that anti-PD-L1 antibodies can be used to treat cancer, and otherwise denies the allegations of Paragraph 12.

PARTIES

13. Genentech admits, on information and belief, that Plaintiff Bristol-Myers Squibb Co. ("BMS") is organized under the laws of the State of Delaware and has a principal place of business at 345 Park Avenue, New York, New York 10154. Genentech admits that the remaining plaintiffs purport to be organized (with respect to the corporate plaintiffs) as alleged, and admits that they purport to have the principal places of business or place of business alleged. Genentech otherwise lacks knowledge or information sufficient to form a belief as to the truth of the remaining allegations in Paragraph 13.

14. Genentech admits the allegations of Paragraph 14, except that the description of Genentech's business, while accurate, is not complete.

15. Genentech admits the allegations of Paragraph 15.

JURISDICTION AND VENUE

16. Genentech admits that this civil action purportedly arises under the Patent Laws of the United States, 35 U.S.C. § 271 et seq., and denies the remainder of the allegations, including any allegations of patent infringement.

17. Genentech admits that this Court would have subject matter jurisdiction over actions arising under the patent laws if standing requirements are met. Genentech denies any remaining allegations of Paragraph 17.

18. Genentech admits that this Court has personal jurisdiction over Genentech for purposes of this action.

19. Genentech admits that venue is proper in this district for purposes of this action.

THE PATENT-IN-SUIT

20. Genentech admits that, on August 2, 2016, the USPTO issued the ’899 patent, which is entitled “Immunopotentiative Composition,” but denies that the ’899 patent is valid. Genentech further admits that Exhibit 1 is a copy of the ’899 patent. Genentech denies that the inventors listed on the face of the ’899 patent “showed for the first time that anti-PD-L1 antibodies were useful in methods to treat cancer.” Genentech admits that on the face of the patent, Dr. Tasuku Honjo is listed as a co-inventor and original assignee and that Ono Pharmaceutical Co., Ltd. (“Ono”) is listed on the face of the ’899 patent as an original co-assignee. Genentech lacks knowledge or information sufficient to form a belief regarding the truth of the remaining allegations of Paragraph 20 and on that basis denies those allegations.

21. Genentech admits that the ’899 patent lists on its face in the Related U.S. Application Data and Foreign Application Priority Data sections the applications identified in Paragraph 21, but lacks knowledge or information sufficient to form a belief regarding whether

Plaintiffs intend to claim priority for all asserted claims to any particular application, and denies that the '899 patent is entitled to such priority.

22. Genentech states that the claims of the '899 patent speak for themselves and admits that claim 1 of the '899 patent is recited in Paragraph 22. Genentech otherwise denies the allegations of Paragraph 22.

GENENTECH'S TECENTRIQ® (ATEZOLIZUMAB)

23. Genentech admits that it or a subsidiary is marketing, distributing, offering for sale, selling, and/or importing Tecentriq®, an anti-PD-L1 antibody, in the United States and incorporates the full prescribing information for Tecentriq® for a complete statement concerning Tecentriq's approved indications. Genentech denies the remainder of the allegations of Paragraph 23.

24. Genentech incorporates the full prescribing information for Tecentriq® for a complete statement concerning Tecentriq's approved indications and administration instructions, admits the allegations of Paragraph 24 to the extent they are consistent with the prescribing information, and otherwise denies them.

25. Genentech admits that the active ingredient in Tecentriq® is atezolizumab, that atezolizumab is an anti-PD-L1 antibody, that atezolizumab is a humanized IgG1 monoclonal antibody, and that, among other things, atezolizumab binds human PD-L1 and blocks its interaction with PD-1. As explained in the label, this "releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity." Genentech denies any remaining allegations of Paragraph 25.

Plaintiffs Allege That The Use of Tecentriq® Infringes the '899 Patent

26. Genentech admits it or a subsidiary is currently distributing, offering for sale, selling, and/or importing Tecentriq® in the United States to be prescribed and used for the treatment of cancer according to Tecentriq's prescribing information. Genentech denies the remaining allegations of Paragraph 26.

27. Genentech admits that Tecentriq® is an anti-PD-L1 monoclonal antibody that, among other things, inhibits an interaction between PD-1 and PD-L1, admits that Tecentriq® is indicated for use in treating patients diagnosed with certain types of cancers, and admits that when Tecentriq® is used as indicated in the prescribing information, it has been shown to have efficacy in certain patients as set forth in the prescribing information. Genentech otherwise denies the allegations of Paragraph 27.

28. Genentech admits that Tecentriq® has been and is currently being used according to the prescribing information, but Genentech denies that such usage infringes claim 1, or any other claims, of the '899 patent. Genentech denies any remaining allegations of Paragraph 28.

29. Genentech admits that atezolizumab is a humanized antibody, but Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 2, 20, or 43, or any other claims, of the '899 patent. Genentech denies any remaining allegations of Paragraph 29.

30. Genentech admits that Tecentriq® has been approved for use in treating patients diagnosed with certain types of cancers (including certain solid tumors) as indicated in the prescribing information for Tecentriq®, which Genentech incorporates here, but Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 3, 21,

or 37, or any other claims, of the ’899 patent. Genentech denies any remaining allegations of Paragraph 30.

31. Genentech admits that Tecentriq® is indicated for the treatment of patients with: locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, or have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy; or metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy, as set forth in the prescribing information. Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 4 or 19, or any other claims, of the ’899 patent. Genentech denies any remaining allegations of Paragraph 31.

32. Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 5, 22, or 36, or any other claims, of the ’899 patent, and otherwise denies the allegations of Paragraph 32.

33. Genentech admits that Tecentriq® has been approved for use in treating patients diagnosed with certain types of cancers as indicated in the prescribing information for Tecentriq®, which Genentech incorporates here, but Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 6-9, 12, 23-26, 29, 38-42, or 44-45, or any other claims, of the ’899 patent. Genentech denies any remaining allegations of Paragraph 33.

34. Genentech admits that Tecentriq® is approved for administration by intravenous infusion, but Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 16 or 33, or any other claims, of the ’899 patent. Genentech denies any remaining allegations of Paragraph 34.

35. Genentech admits that atezolizumab is an IgG1 antibody, but Genentech denies that usage of Tecentriq® according to the prescribing information infringes claims 46-51, or any other claims, of the '899 patent. Genentech denies any remaining allegations of Paragraph 35.

36. Genentech denies the allegations of Paragraph 36.

37. Genentech admits the allegations of Paragraph 37.

38. Genentech admits that atezolizumab is described in U.S. Patent No. 8,217,149 ("the '149 patent"), which is assigned to Genentech and entitled "Anti-PD-L1 Antibodies, Compositions and Articles of Manufacture."

39. Genentech admits that atezolizumab is the active ingredient in Tecentriq®, and that atezolizumab is covered by one or more claims of the '149 patent.

40. Genentech admits that it has known about the '899 patent since approximately August 2016, but denies that Genentech infringes any valid claim of the '899 patent. Genentech refers to the documents cited in Paragraph 40 for their contents and denies any allegations inconsistent with those contents. Genentech further denies that EP878 discloses methods of treating tumors with anti-PD-L1 antibodies. Genentech otherwise denies the allegations of Paragraph 40.

41. Genentech admits that one or more claims of the '104 PCT cover atezolizumab, and, on information and belief, admits that the search report referred to in Paragraph 40 states that it was mailed on April 29, 2010, but denies that it was received on April 29, 2010. Genentech refers to the search report and the documents discussed therein for their contents and denies any allegations inconsistent with those contents. Genentech otherwise denies the allegations of Paragraph 41.

42. Genentech denies the allegations of Paragraph 42.

COUNT I: ALLEGED INFRINGEMENT OF U.S. PATENT NO. 9,402,899

43. Genentech incorporates by reference its responses to Paragraphs 1-42 as if fully set forth herein.

44. Genentech admits that it or a subsidiary is marketing, selling, offering for sale, and/or importing Tecentriq® (atezolizumab) in the United States for the treatment of certain cancers pursuant to Tecentriq's prescribing information. Genentech denies the remainder of the allegations of Paragraph 44.

45. Genentech denies the allegations of Paragraph 45.

46. Genentech denies the allegations of Paragraph 46.

47. Genentech denies the allegations of Paragraph 47.

PLAINTIFFS' JURY DEMAND

Genentech acknowledges that the Complaint purports to set forth a demand for trial by jury on issues so triable.

GENENTECH'S RESPONSE TO PLAINTIFF'S PRAYER FOR RELIEF

Genentech denies all remaining allegations not specifically admitted herein and denies that Plaintiffs are entitled to any of the relief they have requested or to any relief at all.

AFFIRMATIVE AND OTHER DEFENSES

Without assuming any burden other than those imposed by operation of law, and without admitting that it bears the burden of proof with respect to any of the following, Genentech alleges as follows from the facts presently known to it, while reserving the right to add additional defenses based on facts learned in discovery or otherwise.

First Defense
(Failure to State a Claim)

The Complaint fails to state a claim upon which relief can be granted.

Second Defense
(Non-Infringement)

Genentech is not infringing and has not infringed any valid and enforceable claim of the ’899 patent, either directly, contributorily, by inducement, or willfully.

Third Defense
(Invalidity)

Each and every asserted claim of the ’899 patent is invalid for failing to comply with one or more requirements of the patent laws of the United States, including but not limited to, 35 U.S.C. §§ 101, 102, 103, 112 and/or 116, and/or judicially created bases for invalidation based at least upon the facts alleged in the Complaint, Genentech’s Answer to the Complaint, and below in Genentech’s Counterclaims. For example, and without limitation, the asserted claims of the ’899 patent are invalid as anticipated by each of U.S. Patent No. 7,101,550; international patent application WO 01/14557; U.S. Patent No. 7,794,710; and Dong *et al.*, “Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion,” Nature Medicine, vol. 8, issue 8, pp.793-800 (2002), or are rendered obvious by these references, alone and in combination with these references and other references identified below. Furthermore, for example, and without limitation, the claims of the ’899 patent are invalid under Section 112 at least for lack of written description and/or for lack of enablement because the ’899 patent seeks to claim a broad genus, yet by disclosing only one rat anti-mouse PD-L1 monoclonal antibody, the patent fails to describe sufficient representative species encompassing the breadth of the genus and fails to teach how to make and use the full scope of the claimed invention without undue experimentation.

Fourth Defense
(Lack of Standing)

On information and belief, one or more of the Plaintiffs lack standing to assert infringement of the '899 patent, and/or Plaintiffs lack standing to assert the '899 patent in this action because they do not own all rights to that patent.

Fifth Defense
(Prosecution History Estoppel and Prosecution Disclaimer)

Plaintiffs' claims are barred, in whole or in part, under the doctrine of prosecution history estoppel and/or prosecution disclaimer.

Sixth Defense
(Statutory Bar Concerning Uses by the United States)

To the extent that the alleged invention(s) have been used by the United States, Plaintiffs' claims for relief are barred by 28 U.S.C. § 1498.

Seventh Defense
(Safe Harbor)

Plaintiffs' claims for relief are limited by 35 U.S.C. § 271(e).

Eighth Defense
(No Costs)

Plaintiffs are not entitled to seek recovery of their costs pursuant to 35 U.S.C. § 288.

COUNTERCLAIMS

Genentech for its Counterclaims against Bristol-Myers Squibb Co. ("BMS"), E. R. Squibb & Sons, L.L.C. ("Squibb"), Ono Pharmaceutical Co., Ltd. ("Ono") and Tasuku Honjo (collectively, "Counterclaim-Defendants") alleges as follows:

The Parties

1. Genentech is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1 DNA Way, South San Francisco, California 94080. Genentech is widely considered to be one of the founders of the modern field of biotechnology, and has developed many successful and ground-breaking therapeutics, including, for example, Rituxan® (rituximab), Herceptin® (trastuzumab), and the immunotherapy drug Avastin® (bevacizumab).

2. On information and belief, BMS is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 345 Park Ave., New York, New York 10154.

3. On information and belief, Squibb is a limited liability company organized and existing under the laws of the State of Delaware, with its principal place of business at Route 206 & Province Line Road, Princeton, New Jersey 08543.

4. On information and belief, Ono is a corporation organized under the laws of Japan, with its place of business at 8-2 Kyutaromachi 1-chome, Chuo-ku, Osaka 541-8564, Japan.

5. On information and belief, Dr. Honjo is a Japanese citizen who resides in Japan.

Jurisdiction and Venue

6. To the extent the Court has subject matter jurisdiction over the Complaint, it likewise has jurisdiction over the subject matter of these Counterclaims pursuant to 28 U.S.C. §§ 1331, 1338, 2201, and 2202.

7. This Court has personal jurisdiction over Counterclaim-Defendants at least by virtue of the Complaint they filed in this Court.

8. This venue is proper pursuant to 28 U.S.C. §§ 1391 and 1400 because, among other things, Counterclaim-Defendants have asserted a Complaint for patent infringement in this judicial district, in response to which these Counterclaims are being asserted.

The '899 Patent

9. The '899 patent is invalid. The named inventors of the '899 patent (Tasuku Honjo, Nagahiro Minato, Yoshiko Iwai, and Shiro Shibayama, collectively, the "Honjo Inventors") were not the first to describe the possible role of an antibody to PD-L1 in treating cancer, nor were they the first to possess such an antibody. They distinguished their purported invention from the prior art by declaring that they were claiming only methods of treatment using antibodies to PD-L1 that inhibit the interaction between PD-1 and PD-L1, but anti-PD-L1 antibodies that inhibit the interaction between PD-1 and PD-L1 were already known in the art.

10. Furthermore, the Honjo Inventors themselves possessed only one anti-PD-L1 antibody, and they did not even demonstrate that it inhibits an interaction between PD-1 and PD-L1. The Honjo Inventors claimed a broad range, or genus, yet they possessed at most only one possible example, or species, within that genus, and they provided no description of any structure common to the species of the genus so that a skilled artisan could recognize the contours of that genus.

The Use of Anti-PD-L1 Antibodies To Treat Cancer Was Known and Disclosed Prior to the Date of the Honjo Patents

11. Before the priority date for the '899 patent, the use of anti-PD-L1 antibodies to treat cancer was known and disclosed, including in many printed publications and patent applications, including applications that led to issued U.S. patents. Some of the researchers involved in this work were associated with the Dana Farber Cancer Institute (including Gordon

Freeman, Clive Wood, and Arlene Sharpe), while others were associated with the Mayo Clinic (including Lieping Chen and Haidong Dong).

12. Prior art printed publications, prior art published patent applications, and prior art issued U.S. patents that disclosed what the Honjo Inventors sought to claim include:

a. Freeman *et al.*, "Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation," J. Exp. Med. 192(7):1027-1034 (2000) ("Freeman 2000"). In this article, published in October 2000, Drs. Freeman and Wood, publishing with Drs. Honjo and Iwai and others, disclosed *inter alia* that PD-L1 binds to PD-1, that PD-L1 is expressed on some cancers, that PD-L1 signaling can inhibit T-cell proliferation, and suggested "the possibility that some tumors may use *PD-L1* to inhibit an antitumor immune response."

b. Latchman et *al*., "PD-L2 is a second ligand for PD-1 and inhibits T cell activation," *Nature Immunology*, vol. 2, no. 3, pp. 261-268 (March 2001) ("Latchman 2001"). In this article, published in March 2001, Drs. Freeman, Wood, and Sharpe, publishing with Drs. Honjo and Iwai and others (including lead author Yvette Latchman) disclosed, among other things, that "[b]ecause PD-L1 and PD-L2 can inhibit effector T cell proliferation and cytokine production, the PD-L–PD-1 pathway may be an attractive therapeutic target," and that "[b]locking the PD-1 pathway may enhance anti-tumor immunity."

c. International patent application WO 01/14557 (the "Wood '557 PCT") and issued United States Patent No. 7,101,550 (the "Wood '550 patent"), both of which claim priority to a date before the Honjo Inventors' purported inventions. In this application and patent, Drs. Wood and Freeman taught that an antibody to PD-L1 that inhibits the interaction between PD-1 and PD-L1 could be useful for treating tumors. Among other things, they

specifically disclosed that the interaction between PD-1 and PD-L1 can be modulated in order to modulate the immune response. They also showed inhibition of the binding of human PD-L1 to human PD-1 by antibodies to human PD-L1. Drs. Wood and Freeman further described treating a condition that would benefit from upmodulation of the immune systems—tumors being specifically called out as an example—by administering an anti-PD-L1 antibody that interrupted the binding of PD-L1 to PD-1 and thus inhibited the PD-1 signaling pathway. Drs. Wood and Freeman further described that modulation of the PD-1/PD-L1 pathway has an immunoregulatory effect *in vivo*.

d. Carreno and Collins, "The B7 Family Of Ligands and Its Receptors: New Pathways for Costimulation and Inhibition of Immune Responses," Annu. Rev. Immunol. 20:29-53 (2002) ("Carreno & Collins"). In this article, published prior to the priority date for the '899 patent, Drs. Carreno and Collins disclosed, among other things, that PD-L1 transcripts had been detected in various tumor cell lines, that cell-surface expression of PD-L1 had been reported in human breast cancer cell lines, and that tumors may escape the immune response by attenuation of T cell responses upon PD-1 engagement. They further disclosed that "one would predict that blockade of PD-1/PD-L interactions could enhance tumor-specific T cell responses."

e. Dong *et al.*, "B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion," Nature Medicine, 5(12):1365-1369 (1999). In this article, published in December 1999, Drs. Dong, Chen, and others published the first discovery of what is now known to be PD-L1, which they called B7-H1. Their results indicated that PD-L1 "may be involved in the negative regulation of cell-mediated immune responses."

f. United States Patent No. 7,794,710 (the "Chen '710 patent"), issued to Lieping Chen and Scott Strome. This patent discloses and claims methods of inhibiting tumor

cell proliferation in a subject by administering to the subject an antibody that binds to PD-L1. The priority date of the '710 patent is before the date of the Honjo Inventors' claimed invention. The Chen '710 patent discloses, among other things, that interfering with the interaction between PD-L1 and T cells reversed the negative regulatory effect of PD-L1 on T cells and thus enhanced T cell responsiveness, and showed expression of human PD-L1 in human tumor cell lines. The Chen '710 patent further disclosed PD-1 as a T-cell receptor for PD-L1.

g. Dong *et al.*, "Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion," Nature Medicine, vol. 8, issue 8 (2002), pp. 793-800 ("Dong 2002"). In this article, published online on June 24, 2002, Drs. Chen and Dong and others published results including *in vitro* and *in vivo* data showing that an anti-PD-L1 antibody can restore the anti-tumor activity of T cells.

h. Iwai, *et al.*, "Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade," PNAS, vol. 99, no. 19, pp. 12293-12297 (2002) ("Iwai 2002"). In this article, which is prior art to the '899 patent because the '899 patent is not entitled to claim priority to Japanese application 2002-194491, Dr. Iwai, publishing with other Honjo Inventors as well as other scientists, states "present results suggest strongly that effective blockade of PD-1–PD-L1 interaction *in vivo* should provide a promising strategy of immunotherapy for selected tumors expressing PD-L."

13. These are only some of the many references that disclose, prior to the priority date of the '899 patent, what the Honjo Inventors sought to claim in that patent.

The '899 Patent and Its One Anti-PD-L1 Antibody

14. The '899 patent, entitled "Immunopotentiative Composition," issued on August 2, 2016.

15. Claim 1 of the ’899 patent is illustrative, and is directed to “A method of treating a tumor in a human patient in need thereof comprising administering to the human an effective amount of an anti-PD-L1 monoclonal antibody that inhibits an interaction between PD-1 and PD-L1, wherein the anti-PD-L1 monoclonal antibody treats the tumor in the patient.”

16. The ’899 patent does not disclose any anti-human PD-L1 monoclonal antibodies.

17. The ’899 patent references only one anti-PD-L1 antibody: a rat antibody against murine PD-L1, referred to in the patent as clone 1-111.

18. The only *in vivo* test results in the ’899 patent involving an anti-PD-L1 monoclonal antibody are tests in mice, involving transplantation of cell lines or tumors into mice and administration of an anti-PD-L1 antibody to those mice.

19. The ’899 patent does not disclose whether clone 1-111 interfered with the interaction of murine PD-1 and murine PD-L1. The ’899 patent also does not demonstrate that clone 1-111 interfered with the interaction of the PD-1 of any other species and the PD-L1 of any other species.

20. On information and belief, clone 1-111 is not and has never been made, used, sold, offered for sale, or imported into the United States to treat any human patients in accordance with the method described in claim 1 of the ’899 patent.

21. On information and belief, Plaintiffs and Counterclaim Defendants do not make and have never made an anti-PD-L1 antibody that has been approved by the FDA to treat a human patient in accordance with the method described in claim 1 of the ’899 patent.

22. On information and belief, Plaintiffs and Counterclaim Defendants have not commercialized any of the purported inventions of the ’899 patent.

23. On information and belief, Plaintiffs and Counterclaim Defendants are not currently conducting any clinical trial using any anti-PD-L1 monoclonal antibody to practice any of the claimed methods of the ’899 patent.

24. The Honjo Inventors claim inventions in the ’899 patent that are not entitled to claim priority to the 2002 and 2003 Japanese patent applications.

COUNT I — DECLARATORY JUDGMENT OF INVALIDITY: ANTICIPATION

25. Genentech incorporates by reference all previous paragraphs in its Counterclaim as though fully set forth herein.

26. An actual dispute and justiciable controversy exists between the parties as to the validity of the ’899 patent.

27. The claims of the ’899 patent, including at least claims 1-9, 12, 16, 18, 19-26, 29, 33, 35, and 36-51 of the ’899 patent, are invalid for failing to comply with one or more requirements of 35 U.S.C. § 102.

28. The claims of the ’899 patent are generally directed to methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1.

29. The claims of the ’899 patent are invalid under Section 102 at least because, among other reasons, including ones that may come to light during discovery, the claimed methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1 were not novel.

30. For example, the ’899 patent is anticipated by and/or derived from the work of Drs. Freeman, Wood, and/or Sharpe, including as set forth in the Wood ’557 PCT and the Wood ’550 patent. Each such reference discloses methods of treating tumors and/or cancer by

administering an anti-PD-L1 monoclonal antibody, including anti-PD-L1 antibodies that inhibit interaction between PD-1 and PD-L1.

31. For example, the ’899 patent is anticipated by the work of Drs. Chen and Dong, including each of the Chen ’710 patent and Dong 2002. Each such reference discloses methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody, including anti-PD-L1 antibodies that inhibit interaction between PD-1 and PD-L1.

32. Genentech requests that the Court enter a declaratory judgment that the ’899 patent is invalid.

COUNT II — DECLARATORY JUDGMENT OF INVALIDITY: OBVIOUSNESS

33. Genentech incorporates by reference all previous paragraphs in its Counterclaim as though fully set forth herein.

34. An actual dispute and justiciable controversy exists between the parties as to the validity of the ’899 patent.

35. The claims of the ’899 patent, including at least claims 1-9, 12, 16, 18, 19-26, 29, 33, 35, and 36-51 of the ’899 patent, are invalid for failing to comply with 35 U.S.C. § 103.

36. The claims of the ’899 patent are generally directed to methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1.

37. The ’899 patent is invalid under Section 103 at least because, among other reasons, including ones that may come to light during discovery, the claimed methods were obvious to a person of ordinary skill in the art as of the earliest possible priority date for the ’899 Patent.

38. For example, the ’899 patent is rendered obvious by the work of Drs. Freeman, Wood, and Sharpe, alone and in combination with the work of others. For example, the Wood

'557 PCT or Wood '550 patent and the antibodies disclosed therein, alone or in combination with such publications as Freeman 2000, Latchman 2001, and/or Carreno & Collins, render obvious methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1. At least these references showed that anti-PD-L1 antibodies can inhibit an interaction between PD-1 and PD-L1, and that such antibodies were useful in the treatment of tumors and/or cancer. From these teachings, and from the perspective of a person of ordinary skill in the art, methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1 were obvious.

39. For example, the '899 patent is rendered obvious by the work of Drs. Chen and Dong, alone and in combination with the work of others, including the Chen '710 Patent and Dong 2002. For example, the Chen '710 patent and Dong 2002, and the antibodies disclosed therein, alone or in combination with such publications as the '550 patent, Freeman 2000, Latchman 2001, and/or Carreno & Collins, render obvious methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1. At least these references showed that anti-PD-L1 antibodies can inhibit an interaction between PD-1 and PD-L1, and that such antibodies were useful in the treatment of tumors and/or cancer. From these teachings, and from the perspective of a person of ordinary skill in the art, methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1 were obvious.

40. For example, the '899 patent is rendered obvious by the Wood '550 patent in combination with the Chen '710 patent and/or Dong 2002. These references render obvious methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody

that inhibits the interaction between PD-1 and PD-L1. At least these references showed that anti-PD-L1 antibodies can inhibit an interaction between PD-1 and PD-L1, and that such antibodies were useful in the treatment of tumors and/or cancer. From these teachings, and from the perspective of a person of ordinary skill in the art, methods of treating tumors and/or cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1 were obvious.

41. Genentech requests that the Court enter a declaratory judgment that the '899 patent is invalid.

COUNT III — DECLARATORY JUDGMENT OF INVALIDITY: SECTION 112

42. Genentech incorporates by reference all previous paragraphs in its Counterclaim as though fully set forth herein.

43. An actual dispute and controversy exists between the parties as to the validity of the '899 patent.

44. The claims of the '899 patent, including at least claims 1-9, 12, 16, 18, 19-26, 29, 33, 35, and 36-51 of the '899 patent, are invalid for failing to comply with 35 U.S.C. § 112.

45. For example, the claims of the '899 patent are invalid under Section 112 at least for lack of written description because, among other reasons, including ones that may come to light during discovery, the '899 Patent seeks to claim a broad genus, yet by disclosing only one rat anti-mouse PD-L1 monoclonal antibody (and for that antibody, failing to disclose whether it in fact inhibited an interaction between PD-1 and PD-L1), the patent fails to describe sufficient representative species encompassing the breadth of the genus.

46. For example, the claims of the '899 patent are invalid under Section 112 at least for lack of enablement because, among other reasons, including ones that may come to light

during discovery, the ’899 Patent seeks to claim a broad genus, yet by disclosing only one rat anti-mouse PD-L1 monoclonal antibody (and for that antibody, failing to disclose whether it in fact inhibited an interaction between PD-1 and PD-L1), the patent fails to teach how to make and use the full scope of the claimed invention without undue experimentation.

47. Genentech requests that the Court enter a declaratory judgment that the ’899 patent is invalid.

DEMAND FOR A JURY TRIAL

Genentech demands a trial by jury on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, for the reasons set forth above, and for such other reasons that may be presented hereafter, Genentech respectfully requests that this Court grant the following relief:

A. The entry of judgment on the Complaint in favor of Genentech, and against Plaintiffs, and the denial of all relief requested therein;

B. The entry of a declaratory judgment that the asserted claims of the ’899 patent are invalid, and the grant of further relief as may be deemed necessary or proper;

C. A finding that this is an exceptional case and an award to Genentech of its attorneys’ fees pursuant to 35 U.S.C. § 285;

D. An award to Genentech of attorneys’ fees, costs, and expenses incurred by Genentech in defending against Plaintiffs’ Complaint and/or in prosecuting the Counterclaims; and

E. An award to Genentech of such other and further relief as the Court deems just and proper.

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October 4, 2017

CERTIFICATE OF SERVICE

I hereby certify that on October 4, 2017, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on October 4, 2017, upon the following in the manner indicated:

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